Patient and caregiver burden associated with caring for a child with Alagille syndrome: Mixed-methods development of health state vignettes

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Introduction

- Alagille syndrome (ALGS) is a rare, genetic cholestatic liver disease occurring in approximately one in 30,000–50,000 live births,[1,2] in which patients often require liver transplantation, a lifelong state that may lead to transplant failure/rejection.
- The most common symptom of ALGS is intractable pruritus, occurring in up to 88% of patients, with other symptoms including jaundice, failure to thrive and xanthomas.[3]
- Pruritus is associated with a significant negative impact on a patient's health-related quality of life (HRQoL), including fatigue, sleep disruption, negative psychosocial effects and reduced productivity.
- Pruritus is considered the most troublesome symptom of ALGS and can warrant liver transplantation even in the absence of liver failure.[3,4]
- To provide access to ALGS treatments, health technology assessment organisations often require economic evaluations of treatment benefit before approving treatments.
- Utility data are often required to support these analyses and represent the value of a particular health state from 0 (equivalent to dead) to 1 (equivalent to full health), reflecting societal preference for a health state.[5]
- Where there are difficulties collecting sufficient data directly from patients, such as in the case of rare diseases like ALGS, the UK's National Institute for Health and Care Excellence (NICE) recommends using alternative methods to derive utility values. Alternative methods can include general public valuation of vignettes using the EQ-5D or the time trade-off (TTO) method.[5,6]
- In the 2022 health technology evaluations manual,[5] NICE states that evaluations should consider all health effects, including the impact on caregivers, when applicable.

Aims

- To develop and validate health state vignettes describing the HRQoL of children with ALGS and their caregivers.
- To estimate utilities for each patient and caregiver health state using EQ-5D-5L and TTO valuation methods.

Methods

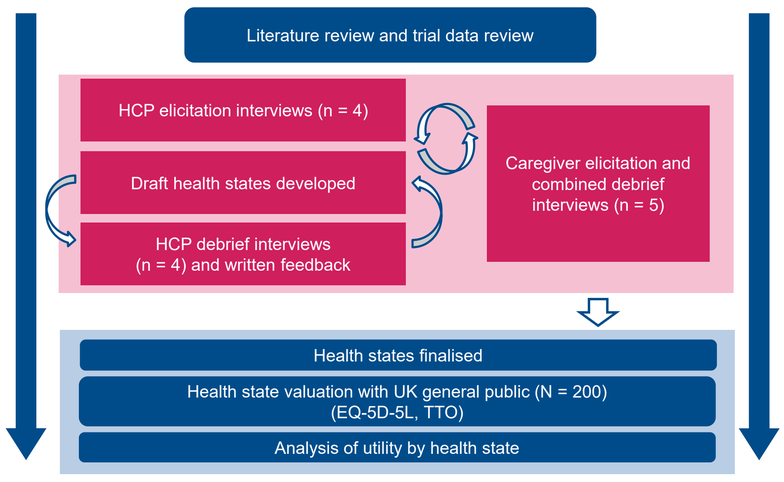
- Figure 1 shows an outline of the health state vignette development methodology.
- Health states were developed using data from a literature review, clinical trial data (ICONIC, NCT02160782) and elicitation interviews with healthcare professionals (HCPs) and caregivers of children with ALGS from the following countries:

HCPs: Canada, France, Italy, Spain

Caregivers of children with ALGS: Canada, UK, USA

- Four health state vignettes were developed to describe:
  - Patients with: progressive cholestasis, non-progressive cholestasis (each defined using serum bile acid [sBA] levels), successful liver transplant and chronic liver transplant rejection.
  - Corresponding caregiver vignettes were also developed; however, caregiver vignettes for two of the health states (non-progressive cholestasis and successful liver transplant) were combined due to limited observed differences in HRQoL impact.
- Health states were reviewed and finalised using debrief interviews with HCPs and caregivers to confirm their accuracy and to identify missing concepts.
- The UK general public (N = 200) provided EQ-5D-5L and TTO ratings for the patient and caregiver vignettes.
- Participants were informed that the health states all described someone with (or a caregiver of someone with) a rare disease that can affect different parts of their body, including their liver, heart, skeleton, eyes and kidneys.
- Example patient and caregiver health states are shown in Figure 2 and Figure 3, respectively.

Figure 1.
Vignette development methodology schematic



HCP, healthcare professional; TTO, time-trade off.

Figure 2.
Patient health state 1 – progressive cholestasis

- You **constantly** experience **severe** itchiness. Scratching has caused skin breakages, bleeding and scars
- You have jaundice, which has caused your eyes to turn yellow
- You experience some **pain and discomfort** from itching
- Your **sleep is disrupted** because of itching
- You **often** feel tired
- You **often** find it difficult to concentrate or focus on a task because of itching
- You need to take **daily** medication and nutrition supplements
- You are able to do your usual activities but **often** have hospital appointments or feel unwell so **sometimes** you have to miss activities
- You have **no problems** with mobility
- You have **no problems** with self-care such as washing and dressing
- You **sometimes** miss social activities when you feel unwell. Due to your visible symptoms, such as jaundice or broken skin, you **often** feel self-conscious about your appearance
- You **often** feel irritable because of itching, which affects your relationships and social interactions
- You **often** feel worried or stressed about your condition and about the future

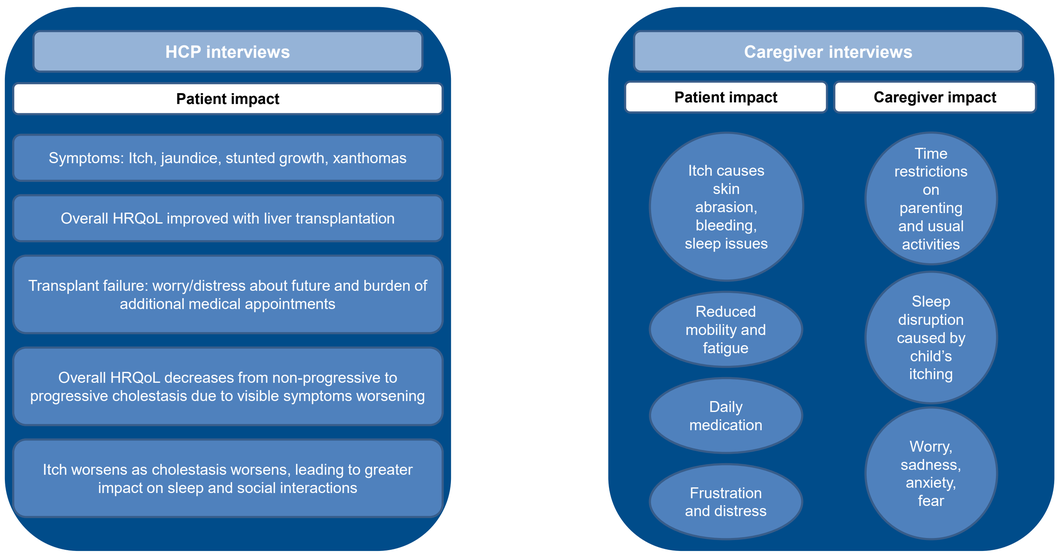
Figure 3.
Caregiver health state 1 – progressive cholestasis

- You are **sometimes able** to do your usual activities, such as work or housework; however, you need to take your family member to **frequent** medical appointments
- You have **limited** time to spend with other family members
- You need to organise your family members' medication and food supplements **every day**
- Your sleep is **frequently disrupted** as the person you care for needs attention multiple times per night
- You **constantly** feel tired
- You have **no pain** or discomfort
- You have **no problems** walking around
- You have **some problems** with self-care due to a lack of time for yourself
- You have **limited time** for social activities with family or friends and have some difficulty integrating with your peers
- You **often** feel stressed due to your caregiving responsibilities
- You **constantly** worry about the family member you provide care for and **sometimes** feel fearful about the future

Results

- Literature review data identified that children with ALGS had poorer global HRQoL and increased fatigue compared with those without ALGS.[4]
- The ICONIC trial's Pediatric Quality of Life Inventory™ (PedsQL 4.0 Generic Core Scales) data identified clinically meaningful improvements in HRQoL.[7]
- Analysis of ICONIC data demonstrated an apparent association between pruritus and HRQoL; thereby showing that successful treatment of pruritus in children with ALGS can have a positive impact on their quality of life.[7]
- A summary of key concepts described in the elicitation interviews with HCPs (n = 4) and caregivers (n = 5) can be found in Figure 4.
- In debrief interviews, caregivers and HCPs largely found health state descriptions accurate. HCPs suggested changes to descriptions of symptoms and emotional impacts. Caregivers also suggested including statements on medication and food administration, tiredness and worry. Changes suggested by both groups were implemented to improve health state accuracy.

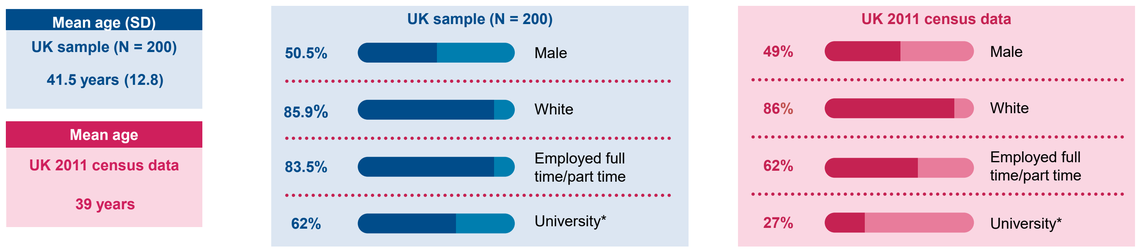
Figure 4.
HCP and caregiver elicitation interviews: Key concepts



HCP, healthcare professional; HRQoL, health-related quality of life.

- A sample of representatives (N = 200) from the UK general public took part in EQ-5D-5L and TTO evaluation interviews, providing ratings for each health state. TTO sample demographics can be found in Table 1.

Table 1.
TTO sample: Sociodemographic information



*This describes the highest level of education achieved by the participant.
SD, standard deviation; TTO, time trade-off.

- Table 2 shows the utility values for the patient health states from the TTO and EQ-5D valuations. The values from the two methods were well aligned; however, EQ-5D values were consistently lower. The utility values for the patient states ranged from 0.506 (EQ-5D: chronic liver transplant rejection) to 0.906 (TTO: successful liver transplant).

Table 2.
Patient health state vignettes: TTO weights and EQ-5D index scores

Health state	Description	TTO weights		EQ-5D index scores	
		Mean (SD)	Range	Mean (SD)	Range
P1	Progressive cholestasis	0.586 (0.397)	–1.000 to 1.000	0.539 (0.192)	–0.311 to 0.893
P2	Non-progressive cholestasis	0.905 (0.173)	–1.000 to 1.000	0.854 (0.072)	0.626 to 0.987
P3	Successful liver transplant	0.906 (0.142)	0.025 to 1.000	0.859 (0.062)	0.483 to 0.989
P4	Chronic liver transplant rejection	0.609 (0.420)	–1.000 to 0.975	0.506 (0.189)	–0.257 to 0.891

SD, standard deviation; TTO, time trade-off.

- It is assumed that patients in the non-progressive cholestasis health state would not require liver transplantations, while those in the progressive cholestasis health state would.
- Table 3 shows the utility values for the caregiver health states from the TTO and EQ-5D valuations. Consistent with the patient values, the EQ-5D values were lower than the TTO values, ranging from 0.526 (EQ-5D: chronic liver transplant rejection) to 0.900 (TTO: non-progressive cholestasis/successful liver transplant).

Table 3.
Caregiver health state vignettes: TTO weights and EQ-5D index scores

Health state	Description	TTO weights		EQ-5D index scores	
		Mean (SD)	Range	Mean (SD)	Range
C1	Progressive cholestasis	0.751 (0.346)	–1.000 to 1.000	0.543 (0.175)	–0.059 to 0.892
C2	Non-progressive cholestasis/Successful liver transplant	0.900 (0.138)	0.025 to 1.000	0.837 (0.084)	0.338 to 0.987
C3	Chronic liver transplant rejection	0.773 (0.312)	–1.000 to 1.000	0.526 (0.174)	0.084 to 0.935

Non-progressive cholestasis and successful liver transplant states were merged due to the similarity in impacts experienced.
SD, standard deviation; TTO, time trade-off.

- Figure 5 and Figure 6 show the distribution of the data for each health state, demonstrating much greater variability in the TTO and EQ-5D values for the progressive cholestasis and chronic liver transplant rejection states than the other health states.
- No published ALGS utility values are available to allow direct comparison with the results, but published values for states similar to progressive cholestasis show higher utilities than the current study (cholestatic liver disease: 0.68–0.79),[9] perhaps indicating the added burden of ALGS in addition to the cholestasis.

Figure 5.
Health state vignettes: TTO weights boxplot

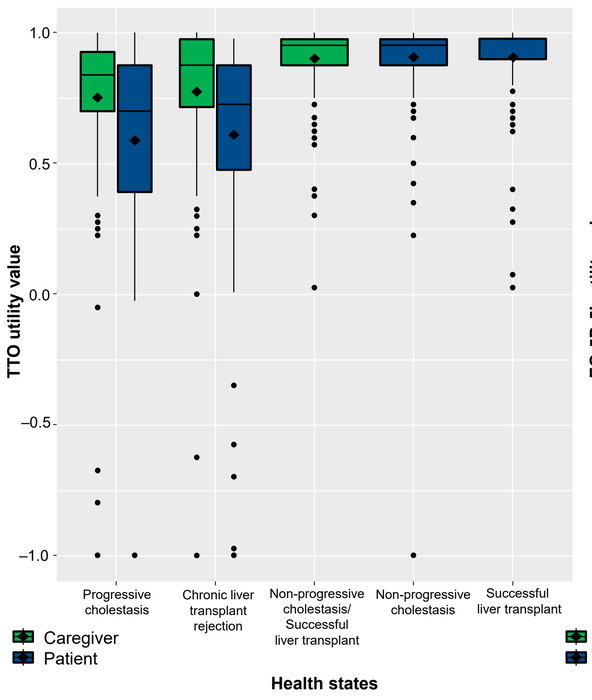
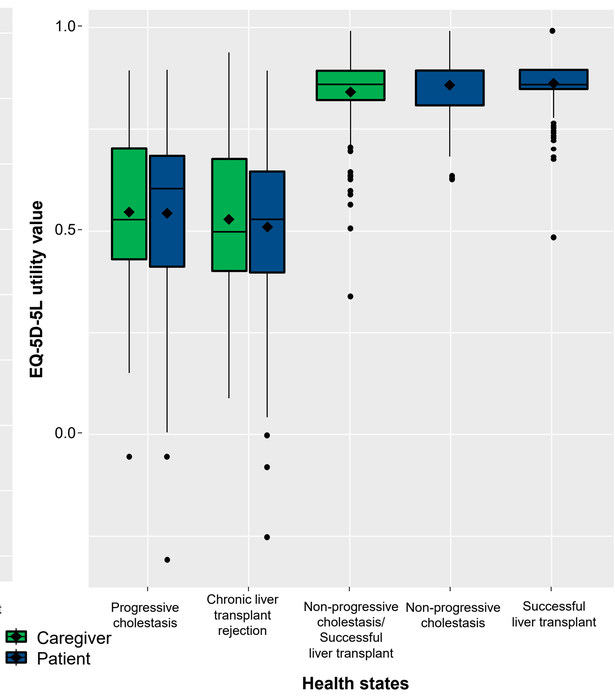


Figure 6.
Health state vignettes: EQ-5D-5L index scores boxplot



TTO, time trade-off.

Conclusions

- **This study demonstrates the effectiveness of a mixed-methods approach to vignette development in generating utility values for use in cost-effectiveness evaluation.**
- **The utility scores obtained in this study demonstrate the burden experienced by children with ALGS and their caregivers caused by cholestasis and liver transplant failure.**
- **Progressive cholestasis results in a significant utility detriment to caregivers and patients using both TTO and EQ-5D preference elicitation approaches.**
- **EQ-5D and TTO utility values generated for progressive cholestasis and chronic transplant rejection are at a similar value for both patient and caregiver health states.**
- **The link between pruritus and sBA shows that in non-progressive cholestasis not only does sBA decrease by 50%, but pruritus can be assumed to be manageable/non-existent as no liver transplants occurred.**
- **Not captured in this study, but based on the correlation between pruritus and sBA, the utility decrement of pruritus in progressive compared with non-progressive cholestasis is likely underestimated; patients would not have pruritus that would require liver transplantation once in the non-progressive health state.**
- **Even successful liver transplants require lifelong monitoring and treatment.**

Contact information

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References

1. Ayoub MD & Kamath BM. Alagille syndrome: diagnostic challenges and advances in management. *Diagnostics (Basel)* 2020;10:907.
2. Sanchez P, Farkhondeh A, Pavlinov I, *et al*. Therapeutics development for Alagille syndrome. *Front Pharmacol* 2021;12:704586.
3. Kamath BM, Baker A, Houwen R, *et al*. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2018;67:148–156.
4. Kamath BM, Chen Z, Romero R, *et al*. Quality of life and its determinants in a multicenter cohort of children with Alagille syndrome. *J Pediatr* 2015;167:390–396:e3.
5. Rowen D, Brazier J, Wong R, *et al*. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. Report by the Decision Support Unit. 31st July 2020. Accessed online at: https://www.sheffield.ac.uk/nice-dsu/methods-development/measuring-health-related-quality-life on 10 October 2022.
6. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Process and methods. [PMG36]. 31 January 2022. Accessed online at: http://www.nice.org.uk/process/pmg36 on 10 October 2022.
7. Kamath BM, Goldstein A, Howard R, *et al*. Maralixibat treatment response in Alagille syndrome is associated with improved health-related quality of life. *J Pediatr* 2022; Epub ahead of print.
8. Dan AA, Kallman JB, Srivastava R, *et al*. Impact of chronic liver disease and cirrhosis on health utilities using SF-6D and the health utility index. *Liver Transpl* 2018;14:321–326.

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Disclosures

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